Quantitative Diffusion-Weighted MR Imaging in the Differential Diagnosis of Parotid Gland Tumors: Is it a Useful Technique?

Parotis Bezi Tümörlerinin Ayırıcı Tanısında Kantitatif Diffüzyon Ağırlıklı Manyetik Rezonans Görüntüleme: Kullanışlı Bir Teknik mi ?

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ABSTRACT Objective: Our purpose was to determine whether the apparent diffusion coefficient (ADC) measurement could be used to identify benign or malignant parotid tumors. **Material and Methods:** In this research 22 patients with 25 parotid gland tumors and 10 controls with 20 healthy parotid glands were studied. Diffusion-weighted magnetic resonance imaging (DW-MRI) with b factors of 0.500 and 1.000 sec/mm^2 on a 1.5 T unit was used. The calculated ADCs values of the parotid gland tumors were compared with histological features of the tumors. **Results:** The study included 25 parotid gland tumors which consisted of 17 benign masses (10 pleomorphic adenomas, 6 Warthin tumors, 1 canalicular adenoma) and 8 malignant masses (4 lymphomas, 2 carcinoma ex pleomorphic adenomas, 1 adenoid cyctic carcinoma, 1 mucoepidermoid carcinoma). The mean ADC values of the control group, benign and malignant masses were 0.27±0.13 x10^{-3} mm^2/sec, 1.51±0.32 x10^{-3} mm^2/sec, 1.05±0.26 x10^{-3} mm^2/sec, respectively ($p<0.001$). A cut-off value at 1.3x10^{-3} mm^2/sec yielded a sensitivity of 87.50% and specifity of 58.82%, for distinguishing benign and malignant masses. **Conclusion:** Our results suggest that quantitative DW-MRI may be used for differentiating benign or malignant parotid gland tumors. Combination of ADC calculation with conventional MRI may have an additional value for determining malignancy.

Key Words: Parotid neoplasms; magnetic resonance imaging; diffusion magnetic resonance imaging

ÖZET Amaç: Bu çalışmadaki amacımız, belirgin difüzyon katsayısı (BDK) ölçümünün parotis bezi tümörlerinin selim ya da habis olduğunu belirlemedeki kullanılabilirliğini belirlemek idi. **Gereç ve Yöntemler:** Bu araştırmada 22 hastadaki 25 parotis tümörü ile kontrol grubunu oluşturan 10 sağlıklı insanın 20 parotis bezi değerlendirilmiştir. b faktörleri 1.5 T'de 0.500 ve 1.000 s/mm^2 olan diffüzyon ağırlıklı manyetik rezonans görüntüleme (DA-MRG) kullanılmıştır. Parotis bezi tümörlerinin BDK değerleri, tümörlerin histolojik özellikleriyle karşılaştırılmıştır. **Bulgular:** Çalışmamız, 17'si selim kitle (10 pleomorfik adenom, 6 Warthin tümörü ve 1 kanaliküler adenom) ve sekizi de habis kitle (4 lenfoma, 2 pleomorfik adenomsuz karsinom, 1 adenoid kistik karsinom ve 1 mukoepidermoid karsinom) olmak üzere toplam 25 parotis bezi tümörünü içermektedir. BDK değerleri ortalamaları kontrol grubunda, selim ve habis tümörlerde sırasıyla 0.27±0.13 x10^{-3} mm^2/s, 1.51±0.32 x10^{-3} mm^2/s, 1.05±0.26 x10^{-3} mm^2/s bulunmuştur ($p<0.001$). Kitlelerin selim ve habis ayırımında 1.3x10^{-3} mm^2/s kesim değeri olarak alındığında duyarlılık %87.5 ve özgüllük %58.82 bulunmuştur.
Sonuç: Çalışmamızdan elde edilen veriler, DA-MRG' nin parotis bezi tümörlerinin selim ve habis ayırımında kullanılabileceğini göstermektedir. BDK değerinin klasik MRG ile kombinasyonu habasetin belirlenmesinde ek katkı sağlayabilmektedir.

Anahtar Kelimeler: Karotis tümörleri; manyetik rezonans görüntüleme; difüzyon ağırlıklı görüntüleme

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Diffusion-weighted imaging (DWI) is a magnetic resonance (MR) technique that provides information about the biophysical properties of tissues such cell organization and density, microstructure and microcirculation. Increased cellular density limits water diffusion in the interstitial space. The apparent diffusion coefficient (ADC), as a quantitive parameter measured from the DW-MRI, combines the effects of capillary perfusion and water diffusion in the extracellular extravascular space. Thus, DW-MRI provides information on perfusion and diffusion simultaneously in any organ. When only high b values are applied, the ADC value approximates the true diffusion. Low b values are influenced by both perfusion and diffusion.[1-4]

Recent studies have shown that DWI with ADC mapping could be used to characterize lesions in a variety of head and neck disorders such as parotid gland tumors.[5,6] The morphology and extent of parotid gland tumors and their relationship to adjacent structures can be clearly shown by MR imaging.[7] However, standard MR imaging sequences usually do not allow differentiating parotid tumors. It is clinically important to determine, whether a salivary gland tumor is benign or malignant preoperatively, which influences the choice of surgical procedure.[8,9]

The aim of our study was to evaluate the diagnostic role of quantitative DWI in various parotid gland masses to differentiate and identify parotid gland tumors.

MATERIAL AND METHODS

PATIENT POPULATION

The study protocol was approved by the local ethics committee. Written informed consents were obtained from all participants. In this prospective study, performed between August 2007 and December 2008, 25 parotid gland masses in 22 patients were examined before fine needle aspiration cytology and surgery and 20 healthy parotid glands in 10 control subjects. The patients [13 men (59.4%) and 9 women (40.6%)] with a mean age of 44 years; (range 18-71 years) and the controls (5 men and 5 women), with a mean age of 50 years; (range 24-70 years) underwent conventional and DW-MRI. Pathological diagnosis of the 20 patients (91%) with parotid tumors was evaluated with fine-needle aspiration biopsy, and remaining 2 (9%) of them with excisional biopsy. Surgical treatment was applied to all cases. Preoperative diagnosis of each mass was compared and confirmed with histopathologic results after resection.

MR IMAGING

All MR examinations were performed on a 1.5 T MRI system with a phased array head and neck coil (Avanto; Siemens, Erlangen, Germany) with a 33 mT/m maximum gradient capability. Our neck MR imaging study included turbo spin-echo (TSE) T1- and T2-weighted, fat-supressed T2-weighted sequences in the axial and coronal plane. For the routine sequences a 5.0-mm section thickness with interslice gap, 35%, a 16x16 cm field of view (FOV), with 3 averages were used. Spin-echo T1-weighted (TR, 383 ms; TE, 9 ms; 256 x 256 matrix), turbo spin-echo T2-weighted (TR, 4400 ms; TE, 109 ms; 250 x 384 matrix) and short tau inversion-recovery (STIR) (TR, 6500 ms; TE, 64 ms; 256 x 256 matrix) images were performed.

Diffusion weighted single-shot spin-echo echo-planar sequence with, chemical shift selective fat-suppression technique; was obtained repetition time (TR) 10.000 ms, echo time (TE) 74.9 ms, matrix, 192 × 192; slice numbers, 30; slice thickness = 5 mm; interslice gap, 35%; FOV, 25 cm; averages, 5; acquisition time, approximately 1 min. 45 s, was performed with b-factors of 0, 500 and 1000 sec/mm² in the axial plane.

Following DWI, contrast enhanced imaging was performed with axial, coronal and sagittal fat-saturated SE T1-weighted MR sequence after administration of gadopentate dimeglumine in a dose of 0.1 mmol/kg of body weight as a bolus injection. The injection rate was 3 mL/sec.

IMAGE ANALYSIS

The DWI datasets were transferred to an independent Workstation (Leonardo console, software version 2.0; Siemens) for post processing, and the ADC

maps were reconstructed. To measure ADC values we applied circular region of interest (ROI) in parotid gland tumors and to the normal parotid glands of the control group. ROI was manually defined in solid areas of tumors excluding the areas of cystic-necrotic degeneration. In the control group each ROI included as much of the gland as possible. The ROI analyses of the healthy gland regions that contained large vessels, such as the retromandibular vein in the parotid gland, were avoided. ADC measurements were performed by 2 radiologists in consensus.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows 15.0. The ADC values of cases were reported as the mean ± standard deviation. In the data analysis of the study, as well as descriptive statistical methods (average, standard deviation); One-way ANOVAs test and post Tukey HSD tests were used in the evaluation of the parameters showing normal distribution evaluated according to three groups. In the evaluation of quantitative data without normal distribution, besides Kruskal Wallis test, Mann-Whitney U-test with the Bonferroni correction was used to determine the group causing differences. To determine the cut-off point according to the ADCs, ROC analysis was applied. Cut-off value was obtained with screening and diagnostic tests (Figure 1, Table 1). Results in 95% confidence interval and the significance in the $p < 0.05$ level were evaluated.

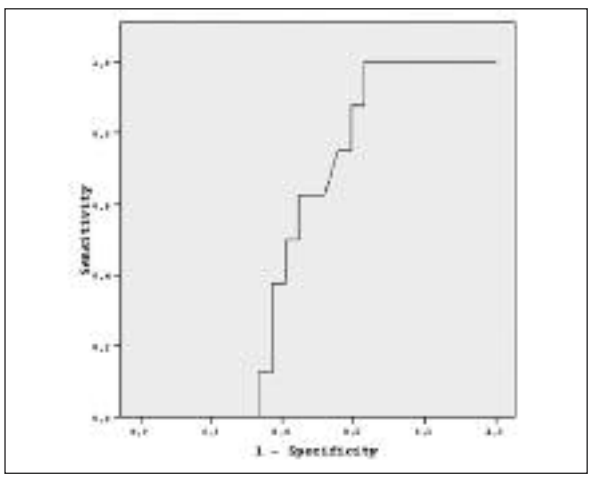

FIGURE 1: ROC curve.

TABLE 1: Determination of the cut-off point for the ADC values.

Value	Sensitivity	Specifity	Positive Predictive Value	Negative Predictive Value
1.58	100.00	52.94	50.00	100.00
1.32	87.50	52.94	46.67	90.00
1.30	87.50	58.82	50.00	90.91
1.29	75.00	58.82	46.15	83.33
1.25	62.50	58.82	41.67	76.92
1.17	62.50	64.71	45.45	78.57
1.02	50.00	64.71	40.00	73.33

RESULTS

The study consisted of 17 benign masses (10 pleomorphic adenomas, 6 Warthin tumors, 1 canalicular adenoma) and 8 malignant masses (4 lymphomas, 2 carcinoma ex pleomorphic adenomas, 1 adenoid cyctic carcinoma, 1 mucoepidermoid carcinoma).

Of 22 cases, 19 were one-sided (86.36%), while remaining 3 cases had two-sided tumors (13.63%). Two of the bilateral tumors were Warthin tumors and one of them was lymphoma.

It was statistically significant when compared with the other groups that all of the malignant tumors in the study were detected in men ($p<0.05$).

The size of 25 masses were between 10-40 mm in the short axis (mean 20.8 mm), 11-44 mm in the long axis (mean 25.92 mm). The long axis measurements of the malignant masses were significantly higher than benign masses ($p<0.05$).

The mean ADC values were calculated for the benign and malignant masses and healthy parotid glands in the control group. The average ADC values were $1.05\pm0.26 \times 10^{-3}$ mm^2/sec for malignant masses, $1.51\pm0.32 \times 10^{-3}$ mm^2/sec for benign masses and $0.27\pm0.13 \times 10^{-3}$ mm^2/sec for healthy parotid glands. There was a significant difference between ADC values of the groups ($p<0.01$).

The mean ADC values for the malignant group were significantly higher than control group

(p=0.001) and significantly lower than benign group (p=0.03). The mean ADC values of the healthy parotid glands in the control group were significantly lower than both malignant and benign groups (p=0.001).

The average ADC values of the control, benign and malignant mass groups and distribution of ADC values according to the pathological diagnosis were listed in Table 2 and 3.

In the benign group of the parotid gland masses, the mean ADC value of the pleomorphic adenomas was significantly higher than the Warthin tumors (p=0.001). Also, the mean ADC value of the pleomorphic adenomas was significantly higher than the malignant tumors (p<0.05).

TABLE 2: Average ADC values of groups.

	ADC		
Groups	**Mean**	**SD**	**†p**
Malignant	1.05	0.26	0.001**
Normal	0.27	0.13	
Benign	1.51	0.32	
		††p	
Malignant – Normal		0.001**	
Malignant - Benign		0.030*	
Normal - Benign		0.001**	

†: Oneway Anova test
††: Tukey HSD test
*p<0.05
**p<0.01

TABLE 3: Distribution of ADC values according to pathological diagnosis.

		ADC	
	Pathological Diagnosis	**Mean**	**SD**
Control group	Normal parotid gland (n=20)	0.27	0.13
Benign	Pleomorphic adenoma (n=10)	1.81	0.34
	Warthin tumor (n=6)	0.91	0.08
	Canalicular adenoma (n=1)	2.02	-
	Total (n=17)	1.51	0.32
Malignant	Carcinoma ex pleomorphic adenoma (n=2)	1.32	0.035
	Mucoepidermoid carcinoma (n=1)	1.17	-
	Adenoid cyctic carcinoma (n=1)	1.29	-
	Lymphoma (n=4)	0.83	0.15
	Total (n=8)	1.05	0.26

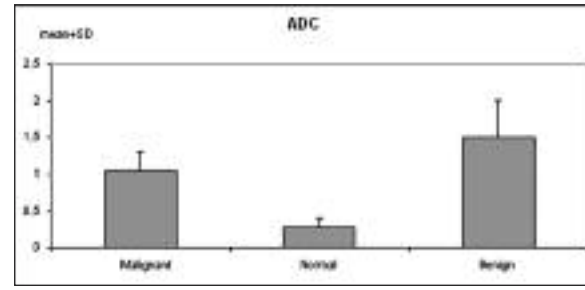

FIGURE 2: Histogram analysis graphic of the average ADC levels.

There was no significant difference between the Warthin tumors and the malignant tumors (p>0.05).

Analysis of the ROC curve (Figure 1) yielded a cut-off point for the ADC value at 1.30 with 87.50% sensitivity, 58.82% specificity, 50% positive and 96% negative predictive values respectively (Table 1).

The histogram analysis of the distribution of groups (Figure 2) and the representative cases were shown in Figures 3-5.

DISCUSSION

DW-MR imaging of the salivary glands has become increasingly popular in the past few years for evaluation of diffuse alterations or circumscribed lesions of the salivary glands. MRI is presently considered the only method available to measure molecular diffusion in vivo. It is important to determine whether a salivary gland tumor is benign or malignant and to know its extent and relationship to adjacent structures preoperatively, since this information will strongly determine for selection the type of surgical procedure.

Conventional imaging techniques alone may not provide adequate information to differentiate a benign lesion from a malignant one.[9] Malignant salivary gland tumors have been reported to have the following MR imaging findings: an irregular tumor margin, signal-intensity heterogeneity, tumor infiltration into surrounding tissue and low signal intensity on T2-weighted images. However, to eliminate malignancy with conventional sequences is quite difficult. In these conditions, quantitative DWI may be a solution.

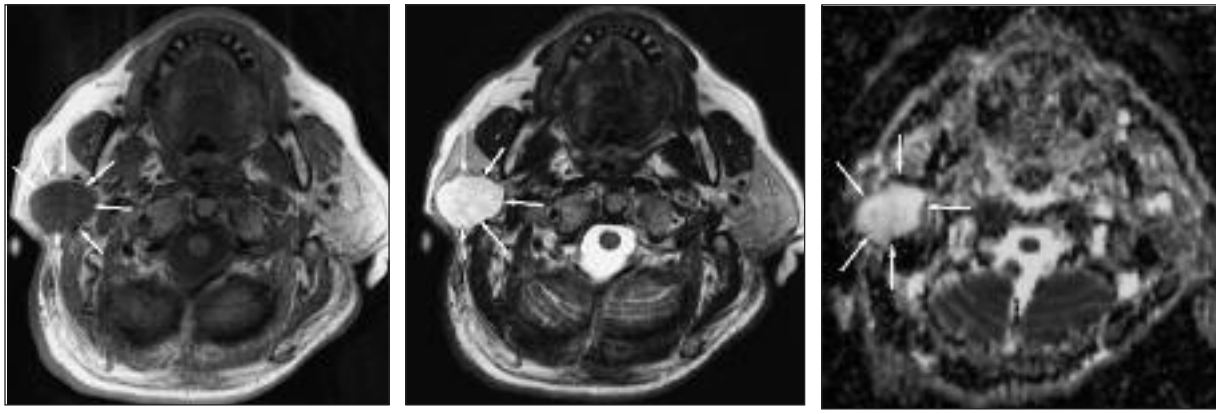

FIGURE 3: Pleomorphic adenoma located in the right parotid gland of a 51-year-old male (white arrows: tumor). **A.** An axial T1-weighted image (TR/TE: 612/12 ms) shows a mass lesion that is more hypointense than gland and isointense in relation to the adjacent muscle. **B.** An axial T2- weighted image (TR/TE: 4320/101 ms) demonstrates anterior displacement and compression of the retromandibular vein by the markedly hyperintense mass. **C.** ADC map reveals that the mass has a high ADC value of 2.18x10-3 mm^2/sec.

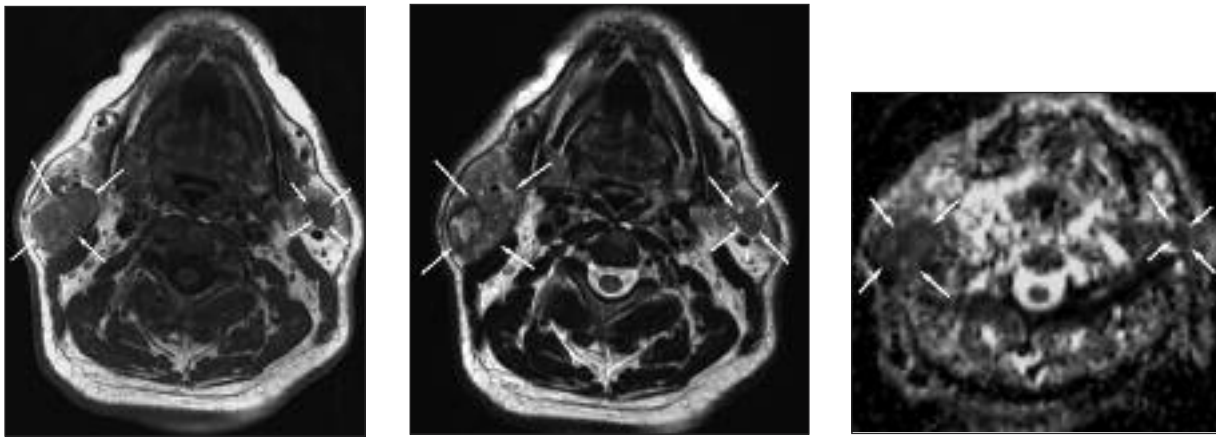

FIGURE 4: Warthin tumor in bilateral parotid glands of a 59-year-old male (white arrows: tumors). **A.** An axial T1-weighted image (TR/TE: 613/12 ms) indicates heterogeneous hypointense mass in the superficial lobe of the right parotid gland extending to the deep lobe of it. Linear hyperintensities of the mass consist of hemorrhage areas. Also smaller, hypointense mass is shown in the left parotid gland. **B.** T2-weighted image (TR/TE: 4460/103 ms) shows heterogeneous masses in bilateral parotid glands with cyctic hyperintense areas. **C.** An ADC image shows bilateral masses with a low ADC value of 0.96x10-3 mm^2/sec.

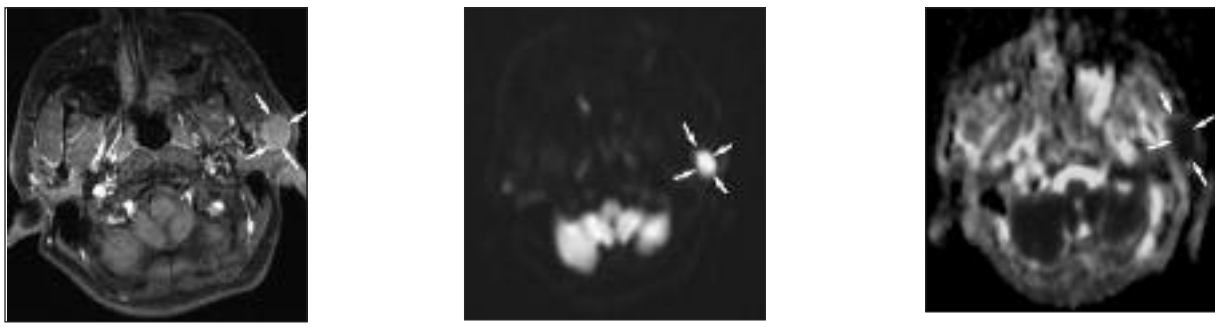

FIGURE 5: Lymphoma of the left parotid gland of a 40-year-old male (white arrows: tumor). **A.** An axial fat saturated post contrast T1-weighted image (TR/TE: 612/12 ms) shows a markedly enhancing mass lesion **B.** The mass is clearly visible on the diffusion-weighted image (b=1000) (TR/TE: 10000/77 ms) with marked hyperintensity **C.** ADC map reveals restricted diffusion and an ADC value of 0.84x10-3 mm^2/sec.

Thoeny et al.[10] used 10 different b factors in their study (0, 50, 100, 150, 200, 250, 300, 500, 750, 1000 s/mm^2), also dealing with the evaluation of different functional conditions of the parotid glands. The ADC values calculated from low b-value settings were significantly higher than those calculated from high b-value settings. Their results have suggested that not only true diffusion but also perfusion and saliva flow may contribute to the ADC. Habermann et al.[11] reported EPI-DW MR technique was useful for discrimination of parotid gland tumors using b-factors (0, 500, 1000 mm^2/sec) in 45 patients. We also used b-factors (0, 500, 1000 mm^2/sec) with EPI technique to create ADC maps.

Water protons can move more freely in the matrix of glandular or mixoid pleomorphic adenomas, therefore, high ADC values can be the indicator of pleomorphic adenomas.[12,13] In our study, the mean ADC value of pleomorphic adenomas was 1.81±0.34 x10^{-3} mm^2/sec. consistent with the literature. This value was significantly higher than the Warthin tumors and the malignant tumors (14.05) ($p<0.05$).

Canalicular adenomas belong to the group of monomorphic adenomas which are benign epithelial tumors that has not mesenchymal component. There was only one canalicular adenoma and its ADC value was 2.02 x 10^{-3} mm^2/sec. This value was significantly higher than the other tumors. Adenomatous tumors may have very high ADC values because of the fluid containing areas as also previously reported by Vogl et al.[14] Moreover, this value is close to the threshold value (2.1 x 10^{-3} mm^2/sec) that was determined by Sakamoto et al.[15] for cystic lesions. In the light of this information, we considered that canalicular adenomas had high ADC values due to their adenomatous structure.

Warthin tumor is the second most common benign salivary gland tumor, which has the highest microvascularity amongst all other parotid tumors. We found the average ADC value as 0.91±0.08 x 10^{-3} mm^2/sec similarly to the previous studies.[11,16]

Habermann et al.[11] demonstrated that the average ADC values of Warthin tumors were lower than mucoepidermoid carcinomas and pleomorphic adenomas. Yerli et al.[13] did not find a significant difference between the average ADCs of Warthin tumors and that of the malignant tumors in their study. Similar to the results of Yerli et al.,[13] the ADCs of Warthin tumors were significantly lower than the other benign tumors and there was no significant difference between the ADC values of Warthin tumors and malignant tumors in our study. We considered it was related to the hypercellularity of the tumor, abundant in lymphoid tissue and limited diffusion of the cystic parts of the tumor due to higher protein content.[13,17]

The malignant tumors in our study were carcinomas (n=4) and lymphomas (n=4). The ADC value of lymphoma is expected to be lower than carcinomas because of its high macromolecular proteinous content and homogeneous hypercellularity narrowing free extracellular space.[18] Mean ADC values of the lymphomas were significantly lower than that of carcinomas in our study. Similar results were also reported by the other researchers.[5,6,15]

Malignant tumors may arise within pleomorphic adenomas, the phenomenon known as carcinoma ex pleomorphic adenoma or malignant mixed tumor which has been reported in 5-10% of cases.[19] It is a high grade tumor with very aggressive course. The mean ADC value of carcinoma ex pleomorphic adenoma was found 1.32 x 10^{-3} mm^2/sec in our study. This value was slightly higher than the cut-off value (1.3 x 10^{-3} mm^2/sec) that we have detected for benign-malignant mass differentiation. However, we were unable to make the statistical evaluation between pleomorphic adenomas and malignant mixed tumor due to insufficient number of patients.

The mean ADC value of the healthy parotid glands in the control group was 0.27±0.13x10^{-3} mm^2/sec. This value was reported as 0.34±0.20x10^{-3} mm^2/sec. by Yerli et al.[13] and 1.14-1.20±0.10x10^{-3} mm^2/sec. by Ries et al.[20] The variability of this value probably depends on the physiological causes.[20] However, all researchers have found that the mean ADC values of the healthy parotid glands were significantly lower than pathological glands. The-

ony et al.[21] reported observations after gustatory stimulation that were completely different from the values observed in the presented study at 1.5T and 3T. At this point, the type of stimulation may have a major impact regarding the different results, which should be evaluated in a prospective study comparing the different stimulation methods. Habermann et al.[22] reported that DW-EPI MR imaging allows monitoring of physiologic changes due to oral stimulation of parotid glands by using DW imaging with high correlation between 1.5T and 3T.

Recent studies in the literature demonstrated that echo-planar imaging technique could be successfully used in the evaluation of head and neck lesions. However, there are some technical difficulties in the DW-MR of the parotid gland. Low signal to noise ratio, chemical shift, magnetic susceptibility and motion artifacts are restrictions of the method.[15,16] To reduce motion artifacts, patients should be warned about not to move their head and swallow. For higher signal to noise ratio, number of excititations (NEX) should be increased. In addition, thinner sections can be made and presaturation bands can be used in the patients with marked distortion artifacts. Our study had some limitations. The main limitation was insufficient number of patients especially in the malignant group. Secondly, we studied only space occupying lesions, in larger series, a comparison with diffuse infiltrating diseases should be made. Lastly single-shot echo-planar imaging used with a higher b-value had a lower SNR resulting in image distortions.

CONCLUSION

Diffusion weighted MR imaging may detect malignancy almost completely; however, some overlaps may occur when the ADC value is used alone. We believe that using ADC values in addition to the conventional sequences may be valuable for differentiation of parotid gland tumors.

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